REMARKS

The Present Invention

The present invention pertains to an isolated or purified metal-containing ribonucleotide protein, a process for producing the same, a medicament comprising the same, and methods related thereto.

The Pending Claims

Claims 8, 9, 11-23 are currently pending. Claims 8 and 11-13 are directed to an isolated or purified metal-containing ribonucleotide protein, claim 9 is directed to a process for producing the same, and claim 14 is directed to a medicament comprising the same. Claims 15-17 are directed to a method of inducing directional growth of a blood vessel in a tissue, claims 18-20 are directed to a method of inducing neovascularization of a tissue, and claims 21-23 are directed to a method of regulating angiogenesis in a tissue.

The Office Action

The Office has alleged that signed declarations for inventors Bridgitte Koch-Pelster and Eckehard Kuhn have not been received. The Office has objected to the drawings, since the margins are purpotedly too small. The Office has deemed the Restriction Requirement proper and, therefore, has made it final. Furthermore, the Office has rejected claim 10 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office has also rejected claim 10 under 35 U.S.C. § 101 as allegedly of improper process claim format. The Office has rejected claims 8 and 9 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description and as allegedly lacking enablement. Reconsideration of the objection and rejections is hereby requested.

The Amendments to the Specification and Claims

The drawings have been amended to make the margins larger and, thus, meet the requirements set forth by 37 C.F.R. §1.84 (g). The specification has been amended to correct the inadvertent typographical errors found within the sequence located on page 3, lines 3-4. Specifically, the sequence now recites "GGAAAAUNNNNNUN$_{0-1}$AUAUGN$_{0-6}$CUNNNUUUNNNNNNAAAAAN$_{0-1}$ UANAAACAUN$_{0-5}$CUUNAGN$_{0-13}$AGAAAUN$_{0-16}$UUAGCAG." This sequence, which, according to page 3, line 3, is the consensus sequence of ARNA I (SEQ ID NO: 3) and ARNA VI (SEQ ID NO: 4), has been amended to correctly express the consensus sequence of both SEQ ID NOs: 3 and 4, which are found in the specification at, for instance, page 3,

lines 11-13 and lines 18-23, respectively. The Sequence Listing also has been amended to reflect the amendment to SEQ ID NO: 2.

Claim 10 has been cancelled. Applicants reserve the right to pursue any canceled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter.

Claim 8 has been amended to recite the phrase "an isolated or purified metal-containing ribonucleotide protein" and is supported in the specification at, for example, pages 5-24. Claim 8 also has been amended to recite "copper ion" and is supported in the specification at, for instance, page 2, line 4. Claim 8 has further been amended to recite "wherein the RPN is" as a matter of form. Claim 8 has also been amended to recite "wherein the RNA has a nucleotide sequence having a consensus nucleotide sequence of SEQ ID NO: 2, and wherein the protein (i) has two EF hand motifs and a zinc(II) ion binding site and (ii) specifically binds to the RNA" and is supported in the specification at, for example, page 3, lines 3 – 7 and page 2, line 14. Claim 8 has been amended to delete the phrases "characterized in that", "of the ternary complex has the following" and "sequences: (a1) ARNA I...[SEQ ID NO: 4]".

Claim 9 has been amended to recite "an isolated or purified RPN" and is supported in the specification at, for instance, pages 5-24. Claim 9 also has been amended to recite "RPN" in lieu of "ribonucleotide protein," as this acronym is set forth in claim 8.

Claims 11-29 have been added. Claim 11 is supported in the specification at, for example, page 3, lines 8-13. Claims 12 and 13 are supported in the specification at, for instance, page 2, lines 6-13. Claims 15-17 are supported in the specification at, for example, page 4, line 23. Claims 18-20 are supported in the specification at, for example, page 4, lines 24 and 25. Claims 21-23 are supported in the specification at, for instance, page 1, lines 13 and 21. Claims 24-29 are supported in the specification at, for example, page 1, line 13. No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the specification and claims, as well as the text of all pending claims, are enclosed herewith.

Discussion of the Signed Oath/Declaration

The Office has alleged that signed declarations for inventors Brigitte Koch-Pelster and Eckehard Kuhn have not been received. Contrary to the Office's assertion, these documents, along with the signed declarations for inventors Stefan Kiesewetter and Herwig Brunner, were mailed on January 16, 2001, via Express Mail and received by the

U.S.P.T.O. Submitted herewith are copies of the signed declarations and a copy of the stamped postcard.

Discussion of the Drawings

The Office has objected the drawings for allegedly having margins that are too small. Submitted herewith are new drawings that meet the requirements of 37 C.F.R. § 1.84(g)

Discussion of the Restriction Requirement

Applicants would like to thank Examiner James Schultz for the telephonic interview, which took place on January 31, 2003, and in which Examiner Schultz agreed to allow into prosecution an independent claim directed to the consensus sequence SEQ ID NO: 2 and claims dependant thereon directed to SEQ ID NO: 3. Accordingly, claim 8 has been amended to read on SEQ ID NO: 2, while claim 11 has been added to be dependent thereon and be directed to SEQ ID NO: 3.

Discussion of the Rejections under 35 U.S.C. § 112, second paragraph, and § 101

The Office has rejected claim 10 under 35 U.S.C. § 112, second paragraph, as allegedly unclear. The Office has also rejected claim 10 under 35 U.S.C. § 101 as allegedly in improper process claim format. In view of the cancellation of claim 10, these rejections are believed to be moot. Applicants, therefore, request that the rejections of claim 10 are withdrawn.

Discussion of the Written Description Rejection

The Office rejects claims 8 and 9 under 35 U.S.C. § 112, first paragraph, as allegedly lacking a written description. Specifically, the Office contends that claim 8 allegedly reads on *any* member of the family of S100 proteins, yet the specification allegedly identifies only one member of the family, namely, that having the amino acid sequence of SEQ ID NO: 1. "The specification fails to identify any other members of said family by any means, including by name, relevant structural characteristics, sequences or important domains or regions of said sequences of proteins," (page 5 of Paper No. 14). The Office further alleges that a representative number of S100 protein family members, including "alleles and variants from species that express said protein and from proteins that retain a function within reasonable functional similarity of said protein family", need to be described in order to claim possession of the entire genus. This rejection is traversed for the reasons set forth below.

The claimed invention must be described in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Electronic, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical,* 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). See M.P.E.P. 2163.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number or species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See the Guidelines for Written Description published at FR 66(4): 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

Contrary to what the Office asserts, the description of the proteins suitable for the instant invention does not stop at the description of the one member of the S100 family of proteins. The specification further details the proteins of the subject ribonucleotide proteins as having two EF hand motifs and a binding site for zinc(II) ions (page 2). The proteins are also described as binding to the RNA part of the ribonucleotide protein (page 5). In this

regard, the invention should not be limited to only the protein having the sequence of SEQ ID NO: 1.

Furthermore, since there are over 900 journal articles published on S100 proteins, the state of the knowledge of the relevant art is such that the number of species needed to be described under the written description requirement would be low, if not one. The level of skill in the art is such that it would require one ordinarily skilled only routine experimentation to identify other S100 proteins that (i) have two ER hand motifs and a zinc(II) ion binding site and (ii) can bind to the RNA portion of the present inventive ribonucleotide proteins. Therefore, although the specification does not list by name or by sequence the other S100 proteins that are suitable for the present inventive ribonucleotide proteins, the specification does provide more guidance that would allow one of ordinary skill in the art to identify these other S100 proteins. Accordingly, claim 8 has been amended to recite the above-described properties of the S100 proteins. Namely, claim 8 now recites "wherein the protein (i) has two EF hand motifs and a zinc (II) ion binding site and (ii) specifically binds to the RNA."

In view of the foregoing arguments and amendments, claim 8 is adequately described, meeting the requirements set forth by 35 U.S.C. § 112, first paragraph. Therefore, Applicants request that this rejection be withdrawn.

Discussion of the Lack of Enablement Rejection

The Office has rejected claims 8 and 9 under § 112, first paragraph, as allegedly lacking enablement. In particular, the Office alleges that, while being enabling for ribonucleotide protein complexes comprising the amino acid sequence of SEQ ID NO: 1 and the nucleic acid sequence of SEQ ID NO: 3, the specification does not enable one of ordinary skill in the art to make and/or use a ribonucleotide protein complex comprising any member of the family of S100 proteins. The Office further alleges that whether or not an interaction between a protein and a RNA molecule exists cannot be determined based on the sequences of the RNA and of the protein alone. The Office continues by arguing that there are no working examples of any ribonucleotide protein complexes other than the one comprising the protein of SEQ ID NO: 1 and the RNA of SEQ ID NO: 3. The Office further contends that the quantity of experimentation required to practice the invention as claimed would require de novo characterization of each S100 family member with the nucleic acid sequence of SEQ ID NO: 3. This rejection is traversed for the reasons set forth below.

The standard question for enablement is whether the experimentation needed to practice the invention is undue or unreasonable. Undue experimentation is evaluated with the following factors (A) breadth of the claims, (B) nature of the invention, (C) state of the prior art, (D) level of one of ordinary skill, (E) level of predictability in the art, (F) amount of

direction provided by the inventor, (G) existence of working examples, and (H) quantity of experimentation needed to make or use the invention based on the content of the disclosure. See, e.g., the U.S. Manual of Patent Examining Procedure (M.P.E.P.) § 2164301.

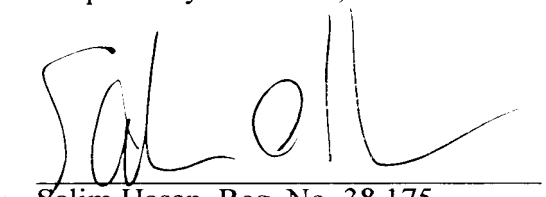
The Office asserts that the specification teaches methods of making and using only one specific ribonucleotide protein. However, this method of isolating and purifying the present inventive RNPs can be applied to other ribonucleotide proteins having an S100 protein other than the one having the sequence of SEQ ID NO: 1. Furthermore, given the level of knowledge and skill in the pertinent art, one of ordinary skill in the art is able to identify the other members of the S100 family that (i) have two EF hand motifs and a zinc(II) ion binding site and (ii) can bind to a RNA molecule of the subject ribonucleotide proteins. In this regard, the claims should not be limited to ribonucleotide proteins having a protein of SEQ ID NO: 1. As claim 8 has been amended to recite *both* of the above properties of the proteins, it would require one of ordinary skill in the art only routine experimentation to determine other S100 proteins that fall within the scope of the claims. For instance, one could simply perform a binding assay to determine which proteins of a cellular homogenate bind to an oligonucleotide having the nucleotide sequence of SEQ ID NO: 3. The proteins that bind could be sequenced to determine if any have two EF hand motifs and a zinc (II) ion binding site. The GenBank Database could then be searched for the sequences of the proteins having two EF hand motifs and a zinc (II) ion binding site to determine if it is a known S100 family member.

In view of the foregoing, the pending claims are enabled. Therefore, Applicants request that the rejection under § 112, first paragraph, for an alleged lack of enablement, be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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PATENT
Attorney Docket No. 206579

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Kiesewetter et al.

Art Unit: 1635

Application No. 09/646,651

Examiner: J. Schultz

Filed: January 16, 2001

For: METAL-CONTAINING
RIBONUCLEOTIDE POLYPEPTIDES

AMENDMENTS TO THE SPECIFICATION AND CLAIMS
MADE IN RESPONSE TO OFFICE ACTION DATED JANUARY 7, 2003

(Deletions are indicated by brackets,
while insertions are indicated by underlining)

Amendments to the specification:

Please replace the paragraph on page 3, lines 3-7, with the following:

The RNA part (ARNA) has the following consensus sequence:
$GGAAAAUNNNNNUN_{0-1}AUAUGN_{0[1]-6}CUNNNUUUNNNNNNAAAAAN_{0-1}$
$UANAAACAUN_{0-5}CUUNAGN_{0-13}AGAAAUN_{0-16}UUAGCAG$
wherein "N" is G, A, U, or C,
or the complementary sequence thereof.

Amendments to claims:

8. (Amended) An isolated or purifed metal-containing ribonucleotide protein (RPN) containing a protein from the family of S100 proteins, an RNA and copper ion, [as metal ion] wherein the RPN is in the form of a ternary complex, wherein [characterized in that] the RNA [of the ternary complex has the following] has a nucleotide sequence having a consensus nucleotide sequence of SEQ ID NO: 2, and wherein the protein (i) has two EF hand motifs and a zinc(II) ion binding site and (ii) specifically binds to the RNA. [sequences:

(a1) ARNA I

Klon-3a (ARNA I)
AAAAAAAAGGUUUUCAUGCGUGCUCACAGAUCAGCUCUUUCUGGAUUGAA
AAGCUAAGCACAGAACAUGGGAAAAUUCCUUUCAUAUGGCUGUGUUUACA
AACAAAAAGUAUAAACAUCUUGAGCAAACAGAAAUGGUGAGGAAAACUUU
GUUAGCAGAUUAG [SEQ ID NO:3]

or

(a2) ARNA VI

Klon-P10 (ARNA VI)
UUACAGCUCUUCUGUUUAUAAGUUAUUCAAUACCAAAUUAGUAGUUUGUA
UGUUAUAAAUUUGUAGGAAAAUAAUUAUAUAUGCUUACUUUGUACAUAAA
AAUAAAAACAUGACUUCUUUAGACACUCCUUCAUUAGAAAUAAAAUAAAA
UAAACUAUUAGCAGUUUGACUUCAUGUUCUGUCUGUAGGUCAUGGAAUCC
UGUCCUUACAAUAUUUAUUGAUUGUGAAAAUAUCAGUAAAUAAGCAAUUG
AAUAUGUUUACCUUUUCUUCUAGUCACUAUGUUCUUAGAGUUAUGACA
[SEQ ID NO:4]]

9. (Amended) A process for producing an isolated or purified metal-containing [ribonucleotide protein (]RPN[)] according to claim 8, characterized in that leucocytes or inflammation tissue is homogenized or leucocytes are cultivated and the resulting RNP is recovered from the homogenates or from the supernatant of the culture solution by standard methods.

10. (Cancelled) [A use of the metal-containing ribonucleotide protein (RPN) according to claim 8 and/or molecular-biological equivalent structures and/or fragments and/or derivatives for producing a medicament for specifically influencing angiogenesis.]

11. (New) The isolated or purified metal-containing RPN of claim 8, wherein the nucleotide sequence having a consensus nucleotide sequence of SEQ ID NO: 2 is SEQ ID NO: 3.

12. (New) The isolated or purified metal-containing RPN of claim 8, wherein the protein has the amino acid sequence of SEQ ID NO: 1.

13. (New) The isolated or purified metal-containing RPN of claim 11, wherein the protein has the amino acid sequence of SEQ ID NO: 1.

14. (New) A medicament comprising the metal-containing ribonucleotide protein (RPN) of claim 8 and/or a molecular-biological equivalent and/or fragment and/or derivative thereof.

15. (New) A method of inducing directional growth of a blood vessel in a tissue, which method comprises administering to a tissue the medicament of claim 14 in an amount sufficient to induce directional growth of a blood vessel in the tissue, whereupon directional growth of a blood vessel in the tissue is induced.

16. (New) The method of claim 15, wherein the tissue is in a mammal.

17. (New) The method of claim 16, wherein the mammal is a human.

18. (New) A method of inducing neovascularization of a tissue, which method comprises administering to a tissue the medicament of claim 14 in an amount sufficient to induce neovascularization of the tissue, whereupon neovascularization of the tissue is induced.

19. (New) The method of claim 18, wherein the tissue is in a mammal.

20. (New) The method of claim 19, wherein the mammal is a human.

21. (New) A method of regulating angiogenesis in a tissue, which method comprises administering to a tissue the medicament of claim 14 in an amount sufficient to regulate angiogenesis in the tissue, whereupon angiogenesis in the tissue is regulated.

22. (New) The method of claim 21, wherein the tissue is in a mammal.

23. (New) The method of claim 22, wherein the mammal is a human.

24. (New) A method of regulating repair of a tissue, which method comprises administering to a tissue the medicament of claim 14 in an amount sufficient to regulate repair of the tissue, whereupon repair of the tissue is regulated.

25. (New) The method of claim 24, wherein the tissue is in a mammal.

26. (New) The method of claim 25, wherein the mammal is a human.

27. (New) A method of regulating wound healing in a tissue, which method comprises administering to a tissue the medicament of claim 14 in an amount sufficient to regulate wound healing in the tissue, whereupon wound healing in the tissue is regulated.

28. (New) The method of claim 27, wherein the tissue is in a mammal.

29. (New) The method of claim 28, wherein the mammal is a human.